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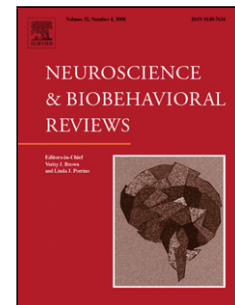
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INHIBITORY CONTROL IN OBESITY AND BINGE EATING DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF NEUROCOGNITIVE AND NEUROIMAGING STUDIES

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Highlights

- Inhibitory control is impaired in obese adults and children compared to controls
- This impairment is independent from the presence of binge eating disorder
- Reduced prefrontal cortex activity affects inhibitory control and BMI

Abstract

The ability to exercise appropriate inhibitory control is critical in the regulation of body weight, but the exact mechanisms are not known. In this systematic review, we identified 37 studies that used specific neuropsychological tasks relevant to inhibitory control performance in obese participants with and without binge eating disorder (BED). We performed a meta-analysis of the studies that used the stop signal task (N=8). We further examined studies on the delay discounting task, the go/no-go task and the Stroop task in a narrative review. We found that inhibitory control is significantly impaired in obese adults and children compared to individuals with body weight within a healthy range (Standardized Mean Difference (SMD): 0.30; CI= 0.00, 0.59, $p=0.007$). The presence of BED in obese individuals did not impact on task performance (SMD: 0.05; CI: -0.22, 0.32, $p=0.419$). Neuroimaging studies in obesity suggest that lower prefrontal cortex activity affects inhibitory control and BMI. In summary, impairment in inhibitory control is a critical feature associated with obesity and a potential target for clinical interventions.

Keywords: inhibitory control, stop signal, go/nogo, prefrontal cortex, obesity, binge eating

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1.0 INTRODUCTION

Obesity is currently considered a global pandemic affecting more than one third of U.S. adults (Ogden et al., 2014; Swinburn et al., 2011) and 13% worldwide, a rate that has doubled since 1980 (World Health Organization, 2015). It is related to increased overall mortality for Alzheimer's disease (Misiak et al., 2012), cancer (Vucenik and Stains, 2012) and heart disease (Lu et al., 2014). Abdominal obesity is also associated with a substantial disease burden with increased risk of type 2 diabetes mellitus and cardiovascular disease (Alberti et al., 2005; Lakka et al., 2002; Lorenzo et al., 2003). Available treatments are often ineffective in modifying the lifestyle and eating behavior that lead to obesity (Fabricatore and Wadden, 2006), therefore the development of innovative treatments that can impact on these domains is now a public health priority.

Binge Eating Disorder (BED) is an eating disorder characterized by recurrent episodes of excessive food consumption accompanied by a sense of loss of control (American Psychiatric Association, 2013). It is the most prevalent type of eating disorder (Hudson et al., 2007) and it affects up to 25% of obese individuals seeking weight-loss treatment (Pull, 2004). Binge episodes have been proposed to be triggered by a breakdown of self-regulation caused by sudden increases in negative affect and tension (Munsch et al., 2012).

Impairment in executive function is consistently found in several neuropsychiatric syndromes (Etkin et al., 2013), including eating disorders (Van den Eynde et al., 2011). Inhibitory control,

one of the fundamental components of executive function, can be operationalized as the overriding of a planned or already initiated action (e.g. responding to a stimulus, or seeking a reward) (Bari and Robbins, 2013). When experiencing strong impulses or urges to eat, a lack of inhibitory control may cause impulsive eating and lead to obesity (Appelhans, 2009). Inhibitory control is experimentally assessed with standardized and validated tests, such as the go/no-go task, stop-signal task (SST), Stroop task and delay discounting task (Chambers et al., 2009). These tasks are thought to measure different facets of inhibitory control. The go-no/go task and the SST are considered typical measures of response inhibition (Chambers et al., 2009). In the go-no/go task, participants are instructed to respond as quickly as possible (e.g. pressing a button) when a frequent *go* signal appears, but must inhibit the response when an infrequent *stop* signal occurs. Inhibitory control performance is assessed based on the percentage of responses to *stop* signals (errors). In the SST, the *go* signal is interrupted in some trials by a *stop* signal presented after it. Participants are instructed to cancel the *go* response when they are shown the *stop* signal. Typically, the more the presentation of the *stop* signal is delayed, the more difficult it is for the participant to withhold the response. This situation is usually interpreted with the *race model* (Logan and Cowan, 1984): whether a participant manages to withhold the response depends on the result of the competition of two independent processes: *go* and *stop*. The stop trial won't be successful (resulting in a failure to inhibit the response) when the *go* process is completed before the *stop* process. Traditionally, the most used outcome measure in the SST is the stop signal reaction time (SSRT). The SSRT is calculated subtracting the stop signal delay (the delay between go and stop signal that allows correct inhibition on approximately 50% of the stop trials) from the mean reaction time (mean reaction

time to a go trial). Shorter the SSRT better the inhibitory performance. The Stroop task is also used as a measure of response inhibition (Potenza et al., 2003), although it has been suggested that other processes such as conflict resolution and response selection could also be involved (Chambers et al., 2009). In a basic version, the Stroop task is comprised of three conditions. In the *reading condition*, the participant reads words written in black ink. In the *color naming condition*, the participant has to name the colors of a series of colored squares. Finally, in the *inhibition condition*, the participant is presented a series of words written in different colors and is asked to name which color the words are written in. The words are printed in an ink that is incongruent with the word (for example, the word 'red' is written in green ink). The participant needs to process task-relevant color information (ink) and inhibit prepotent processing of conflicting task-irrelevant information (word). Performance is measured with completion time (longer response time=worse inhibitory control). In the delay discounting task, poor inhibitory control is defined as the tendency to choose immediate, smaller rewards over larger but postponed ones in a series of trials (steep discounting of value as a function of time). The delay discounting task has been suggested to recruit more affectively charged cognitive processes compared to the previously described response inhibition paradigms (Bari and Robbins, 2013). Inhibitory control as measured in the above laboratory tests is thought to be a relatively stable and general trait which affects several specific domains/contexts (e.g. food intake, smoking or substance abuse)(Bari and Robbins, 2013).

The relationship between inhibitory control, obesity and binge eating has not been fully understood yet. In particular, it is not clear if inhibitory control processes are impaired in obesity in general or more specifically related to binge eating behavior. Since BED has been

associated with high co-morbidity with other psychiatric disorders (Hudson et al., 2007; Kessler et al., 2013) and medical disorders (Javaras et al., 2008), it is important to study the specific neurocognitive mechanisms that characterize it, distinguishing them from those that underlie obesity without BED. Schag et al, in a narrative review, reported that obese participants with BED had increased scores in self-report measures of food-related impulsivity compared with normal weight controls and that impulsivity was more pronounced in BED individuals compared to obese participants without BED (Schag et al., 2013). Other studies found lower inhibitory control performance (as measured by SST) to predict the outcome of a weight loss program in obese children and adolescents (Kulendran et al., 2014; Nederkoorn et al., 2007). Nederkoorn and colleagues specifically assessed binge eating: only 2 children of the 26 who participated in the study had binge episodes. The above findings suggest that dysfunctional inhibitory control could be an underlying cognitive deficit in people who gain weight regardless of binge eating patterns. A systematic assessment of the available literature on inhibitory control tasks in obese individuals with and without BED appears to be indicated to gain a better understanding of this issue.

Several lines of clinical evidence suggest that inhibitory control of eating behavior is regulated by the neural circuitry involving the frontal cortex (Knoch and Fehr, 2007; Szczepanski and Knight, 2014). First, frontal lobe dysfunctions have been shown to be associated with altered eating behaviors (Alonso-Alonso and Pascual-Leone, 2007). Hyperphagia as a clinical sign has been reported in neurologic syndromes that are characterized by frontal lobe impairment such as fronto-temporal dementia (Ikeda et al., 2002; Piguet, 2011; Whitwell et al., 2007), Klein-Levin syndrome (Landtblom et al., 2002) and the “Gourmand syndrome” (Regard and Landis, 1997). Second, hyperphagia and overweight were common in patients who underwent frontal

leucotomy, a surgical procedure that disconnected the frontal lobes from the rest of the brain in an attempt to treat severe mental illness (Freeman and Watts, 1950). Third, frontal lobe dysfunction has been suggested to be the cause of altered eating behavior in Prader-Willi syndrome, a genetic disorder associated with developmental delay, obesity and hyperphagia (Ogura et al., 2008). A recent neuroimaging study comparing obese participants with Prader-Willi syndrome to obese participants without the syndrome found post-meal hypoactivation of the dorsolateral prefrontal cortex (PFC) during response to food vs non-food images (a measure of inhibitory control)(Holsen et al., 2012). Finally, symptoms related to dysfunction of the frontal cortex have also been reported in obesity with BED: for instance, participants with BED showed higher scores in the Frontal Systems Behavior Scale, a measure of neurobehavioral traits associated with the PFC (Boeka and Lokken, 2011).

Functional neuroimaging studies are important to understand the neuroanatomical and functional mechanisms of inhibitory control deficits in obesity and binge eating, and to devise cognitive and brain targets for novel neuromodulatory techniques (Alonso-Alonso, 2013).

The aims of this systematic review and meta-analysis are twofold: a) to evaluate the presence of alterations in inhibitory control performance in obese participants with and without BED; and b) to assess neural correlates of inhibitory control performance in obese participants compared to normal weight controls. Accordingly, the proposed systematic review will address the following questions:

1. Do obese participants have impairments in inhibitory control indexed by performance in specific neurocognitive tests compared to normal weight controls?

2. Do obese participants with binge eating disorder have more severe impairments in inhibitory control compared to obese participants without the disorder?
3. Is neural activation in the prefrontal cortex measured by neuroimaging techniques altered in obese participants compared to normal weight controls during a standard inhibitory control task?

We hypothesize that inhibitory control is impaired in obese participants compared to normal weight controls and in obese participants with BED compared to obese controls; we also expect to find reduced PFC activation during inhibitory control tasks in obese participants compared to controls.

2.0 METHODS

2.1 Search strategy

The review process was conducted according to the principles of the PRISMA-Statement (Liberati et al., 2009; Moher et al., 2009; Shamseer et al., 2015). Searches were conducted up to April 2015; all relevant articles published before the end of April 2015 were considered for inclusion. We did not establish any restrictions on publication date. The PRISMA flow chart for study inclusion is reported in Figure 1. Entire PubMed, EMBASE and PsychInfo were searched for published experimental studies examining group differences in inhibitory control between obese and control participants and between binge eating obese and non-binge eating obese participants. Reference lists of relevant articles were also searched. Search terms were “obesity” AND “go/no-go”; “obesity” AND “stop-signal”; “obesity” AND “delay discounting”;

“obesity” AND “Stroop”; “obesity” AND “inhibitory control”. Search terms that included the Medical Subject Headings (MeSH) terms were based on the following path: (obesity [MeSH] OR overweight [MeSH] OR “binge eating disorder” [MeSH] OR hyperphagia [MeSH] OR “body mass index” [MeSH] OR “binge eating” [Title/Abstract]) AND (“inhibition(psychology)”[mesh] OR “stop-signal” [Title/Abstract] OR “go/no-go” [Title/Abstract] OR “behavioral inhibition” [Title/Abstract] OR “response inhibition” OR “delay discounting” [Title/Abstract] OR “self-regulation” [Title/Abstract] OR “self-control” [Title/Abstract]).

2.2 Eligibility Criteria

The eligibility criteria followed the modified PICOS-criteria (Liberati et al., 2009) and aimed to select overweight/obese individuals of any age with or without BED individuals. Overweight is defined as BMI between 25 and 30; obesity is defined as body mass index (BMI)>30. Case-control studies comparing obese participants and matched participants with normal weight or obese participants with and obese participants without binge eating behaviors were considered. Studies featuring participants with other psychiatric or somatic syndromes capable of affecting weight or eating behavior, such as Prader-Willi syndrome, were excluded. Outcome measures eligible for inclusion were neurocognitive tasks assessing inhibitory control. Given the stated focus of the review on neurocognitive tests and neuroimaging, findings regarding other modalities (e.g. EEG) were not considered for discussion. Qualitative studies that used questionnaires were excluded. An essential element for inclusion was that studies should have clear descriptions of methods used. This search strategy resulted in three categories of studies:

1) adults with obesity and BED; 2) children and adolescents with obesity/overweight (age 6 to 17 years); 3) neuroimaging studies on inhibitory control paradigms in obese participants with and without BED.

2.3 Study selection and data collection

Study eligibility was assessed following the defined eligibility criteria as shown in the flowchart in Figure 1. All results were screened by scanning article titles and abstracts. Duplicate publications were excluded from further analysis.

2.4 Data extraction and quality assessment

Data extraction was operationalized to identify: 1) demographic and clinical characteristics of the study population (age, BMI, male to female ratio); 2) diagnosis (obesity with or without BED); 3) type of neurocognitive test used; 4) description of the results.

Given the lack of standardized criteria for the assessment of neuropsychological studies, we developed a standardized checklist for quality assessment and the identification of risk of bias. The checklist was based on the Newcastle-Ottawa scale (NOS: www.ohri.ca/programs/clinical_epidemiology/oxford.htm). We considered the quality items for the first two domains (`selection` and `comparability`), given that the third domain of the scale (`exposure`) was not pertinent to the studies we considered. Ratings were summed up to a total score with a maximum value of 8: 6 points for sample selection and assessment of

potential for selection biases; 2 points for comparability and controlling for confounding factors. Quality levels of evidence were defined as high (7-8 points); medium (4-6 points) and low (1-3 points).

2.5 Quantitative data synthesis, additional analyses

Statistical analysis as previously described (Arnone et al., 2012, 2009; Selvaraj et al., 2014) was conducted using STATA 11.0 (Stata Corp, College Station, Texas) supplemented by 'Metan' software downloadable from the Centre for Statistics in Medicine, Oxford, UK. Standardised mean differences were calculated using Cohen's d statistic:

$$\text{Cohen's } d = \frac{\bar{X}_1 - \bar{X}_2}{SD_p}$$

Where \bar{X}_1 and \bar{X}_2 are the mean values from the first and second groups, respectively and SD_p is the pooled standard deviation estimated from both groups:

$$SD_p = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{(n_1 + n_2 - 2)}}$$

Where n_i and SD_i are the mean and standard deviation of the ' i th' group. Standardised effect sizes were then combined using the inverse variance method. The variance of Cohen's d is estimated as:

$$SD(d) = \sqrt{\frac{N}{n_1 n_2} + \frac{d^2}{2(N-2)}}$$

Where N is the total sample size for the study, d is Cohen's d and n_1 and n_2 are as defined above. Random effects analyses (DerSimonian and Laird, 1986) were used throughout to weight each study. The presence of heterogeneity was tested using the Q -test and its magnitude estimated using I^2 , which can be interpreted as the proportion of effect size variance due to heterogeneity (Higgins et al., 2003). When the Q -test was significant, we used a Galbraith plot to identify those studies contributing the greatest amount to that heterogeneity, in order to investigate potential causes. Publication bias, which describes the tendency of small studies to report large effect sizes, was examined using the Egger's test (Egger et al., 1997). The significance level was set at $p < 0.05$.

Replicability of the findings was tested by means of sensitivity analyses, which excluded one study at the time to ascertain whether measured effect sizes were influenced by any specific dataset. To further investigate causes for heterogeneity, meta-regression analyses were performed for the following variables: age, sex, BMI, presence of comorbidity, year of publication. The STATA program "metareg.ado" was used throughout with REML (restricted maximum likelihood) method as the default algorithm (Thompson and Sharp, 1999).

3.0 RESULTS

3.1 Study selection

Searches resulted in 1793 eligible studies of which 37 met inclusion criteria. Figure 1 provides a flow chart with reasons for exclusion and Tables 1, 2 and 3 summarize the details of the studies

included. Inhibitory control has shown significant differences in performance between children and young adults (Williams et al., 1999) likely as a consequence of different developmental stages. Therefore, the studies reporting on adults (Table 1) and children and adolescents (Table 2) will be discussed separately.

3.2 Inhibitory control in adults

Overall, 20 studies that investigated differences on inhibitory control performance in groups of adults were included (see Figure 1 for details). The studies included group comparisons between obese participants and individuals with normal weight (N=15) and between obese participants with BED and without BED (N=8) (Table 1). The quality of most studies assessed on the basis of sample selection, thoroughness of reporting and avoiding biases, was scored “medium” for most studies (14 studies), “low” for one study, and “high” for five studies. See Table 1 for details of samples, tasks used and quality scores. The most represented task, used in approximately 35% of the studies (N=7) was the stop signal task (SST). Other tasks reported were delay discounting task, go/no-go task and Stroop task. A significant decrease in inhibitory response performance in any task was evident in obese individuals compared to lean controls in 60% of the reports (N=9), while the remaining studies did not show a significant difference. Conversely, inhibitory control performance was found to be impaired in only 37% of studies on obese participants with BED compared to obese participants without BED (N=3). In one study (Mole et al., 2014) obese participants without BED showed higher stop signal response time,

and therefore greater impairment in inhibitory control, compared to obese participants with BED.

3.3 Meta-analyses

The difference in neurocognitive tasks used did not allow us to include all available results in a quantitative meta-analysis (Table 1). However, it was possible to perform a meta-analysis of the six studies that used the SST task to study differences in inhibitory control performance between obese participants and normal weight controls (Bongers et al., 2014; Chamberlain et al., 2015; Grant et al., 2015; Hendrick et al., 2012; Mole et al., 2014; Nederkoorn et al., 2006), and of the three studies that compared obese participants with BED to obese participants without BED. As shown in Figure 2, we measured a significant impairment in inhibitory control in the obese participants compared to controls, indexed by increases in SSRT, with a Standardized Mean Difference (SMD) = 0.30 (CI: 0.00, 0.59, $p=0.007$), in the absence of publication bias ($p=0.37$). The presence of significant heterogeneity ($p<0.007$) was not explained by the variables we considered in meta-regression analyses (all $p_s>0.05$). The analysis of the obese participants with BED and obese participants without BED groups (Figure 3)(Mole et al., 2014; Svaldi et al., 2014; Wu et al., 2013) indicated the absence of a significant difference between the two groups (SMD: 0.05; CI: -0.22,0.32, $p=0.419$) with no evidence of publication bias ($p=0.89$) or an excess of heterogeneity ($p=0.89$).

Overall, the results of the studies suggest that obese participants without BED had decreased performance in inhibitory control tasks compared to normal weight controls (i.e., higher

reaction times or steeper discounting), while the group comparisons between obese participants with BED and obese participants without BED were not significant.

3.4 Inhibitory control in children and adolescents

Ten studies comparing obese children with normal weight controls met inclusion criteria. The quality score was “medium” in 7 studies and “high” in three studies. The features of the studies are summarized in Table 2. The heterogeneity of the age ranges in the samples was notable, varying between 7 to 9 years (Kamijo et al., 2012; Nederkoorn et al., 2012) and 13 to 19 years (Fields et al., 2011). Since there are relevant age-related differences in inhibitory control, which reflect different developmental stages (Williams et al., 1999), we did not perform a meta-analysis. All the studies included in this category found inhibitory control to be impaired in obese children compared to peers of the same age group.

3.5 Neuroimaging studies of inhibitory control

Given the paucity of neuroimaging studies on overweight/obese participants using inhibitory control paradigms, we decided to include all available neuroimaging studies that investigated the relationship between neural activation related to inhibitory control and BMI to provide a narrative review on neural circuitry involved in inhibitory control in obesity. The quality score was not applied here, since group comparison was not a requirement. Table 3 summarizes the features of the seven neuroimaging studies included and the findings.

Inhibitory control-related activity in regions of the PFC such as the superior frontal gyrus, the middle frontal gyrus and inferior frontal gyrus have been found to correlate inversely with baseline BMI (Batterink et al., 2010; Hendrick et al., 2012) and with subsequent weight increase (Batterink et al., 2010; Kishinevsky et al., 2012; Weygandt et al., 2015, 2013). These findings have been summarized in Figure 4. Activation in other regions that are considered part of an extended inhibitory control network, such as parietal cortex, insula, cuneus, supplementary motor area (Bari and Robbins, 2013; Chambers et al., 2009; Ghahremani et al., 2015; Luijten et al., 2014) were also found to correlate inversely with BMI (Hendrick et al., 2012).

Two studies investigating group differences between obese participants with BED and obese participants without BED found reduced bilateral activation of the PFC during inhibitory control tasks in obese participants with BED (Balodis et al., 2013; Hege et al., 2014).

4.0 DISCUSSION

Our main findings are that there is a decrease in inhibitory control performance in adult obese participants without BED compared to controls and in obese children and adolescents compared to controls. There was no significant difference in inhibitory performance in obese participants with and without BED. Functional neuroimaging of neural activation during inhibitory control tasks in obese participants with BED compared to obese participants without BED reveal a consistent pattern of reduced activation in the PFC. Also, increased BMI is related to a decrease in inhibitory-control related activity in a network where the PFC is the key node (Batterink et al., 2010; Kishinevsky et al., 2012; Weygandt et al., 2015, 2013).

4.1 Behavioral investigations

The available studies with inhibitory control tasks and the meta-analysis of the studies that used the stop-signal test (SST), indicate the presence of inhibitory control deficits in obese participants without BED compared to controls in both adults and children. A recent narrative review which considered selectively the role SST in eating disorders and obesity also concludes that obese individuals may show impaired inhibitory control, although they point out that the results may differ depending on which stimuli are used (Bartholdy et al., 2016). The multidimensional nature of control inhibition and the discrepancy in results based on the technique used to measure this complex construct is also supported by a recent study suggesting a lack of association between BMI and response inhibition (Lawyer et al., 2015). However, our results of inhibitory control deficits in obese participants without BED compared to normal weight controls is consistent with longitudinal studies that found that worse inhibitory control performance is correlated with greater subsequent weight increase (Kulendran et al., 2014; Nederkoorn et al., 2007; Pauli-Pott et al., 2010; Weygandt et al., 2013), and was related to higher food intake in eating laboratory protocols (Appelhans et al., 2011). These results indicate that inhibitory control performance deficits may predict weight increase over time. It is likely that impairments in inhibitory control play a role in resisting the impulse to obtain tasty but unhealthy food, and in effectively downregulating the motivation to consume desirable food: both these functions have been shown to recruit the prefrontal cortex (Hare et al., 2009; Hollmann et al., 2012).

Preliminary studies suggest that specific inhibitory control training can be effective in altering short-term eating behavior in controlled experimental conditions (Houben, 2011; Lawrence et al., 2015; van Koningsbruggen et al., 2014). In van Koningsbruggen et al. (2014), participants receiving two different interventions aimed at potentiating inhibitory control selected respectively 36% and 51% fewer sweets than control participants in a controlled laboratory environment. In a study by Lawrence et al. (2015), a group of participants who were trained to inhibit motor responses to pictures of food ate significantly less calories (-60 kcal; 95%CI=-1.51 to -118.68 kcal), compared to participants that were trained to execute a response to food pictures in an ad-libitum snacking test. Although large scale clinical studies are necessary for confirmation in this patient population, there are encouraging findings pointing to rapid plasticity in inhibition-related brain regions as a result of practice of inhibitory processes (reviewed in Chambers et al., 2009). These studies open up a therapeutic possibility that inhibitory control deficits can potentially be improved and sustained by specific neurocognitive training.

The relationship between inhibitory control and binge eating is less clear. In the studies we examined, obese participants with BED do not seem to show a consistent impairment of inhibitory control compared to obese participants without BED. The meta-analysis considering only the studies that utilized the SST (n=3) does not show a significant difference between the groups (see Figure 3). This could be due to small study bias (we were able to find only 7 such studies, only 3 utilized the SST and were included in the meta-analysis). However, there was no evidence of publication bias in the meta-analysis, nor any significant excess of heterogeneity. This result is consistent with recent reviews reporting no significant differences in inhibitory

control in participants with eating disorders compared to controls (Bartholdy et al., 2016; Van den Eynde et al., 2011). However a recent study by Manasse and others suggests that the use of the Stop Signal Task might be sensitive to elucidating inhibitory deficits in obese individuals with binge eating features although not selective to specific stimuli type (Manasse et al., 2016).

Recently, a psychostimulant (lisdexamfetamine) has been approved for the treatment of BED by the Food and Drug Administration. Lisdexamfetamine appears to result in weight decreases between 5.2% and 6.25% at 50 or 70 mg/day (Citrome, 2015). Psychostimulants are known to facilitate response inhibition by modulating PFC function (Solanto, 1998; Spencer et al., 2001). In addition, successful amelioration or remission of binge eating in participants with BED through treatment with antidepressants (Capasso et al., 2009; McElroy et al., 2012; Reas and Grilo, 2008) or psychosocial interventions (Wilson et al., 2010) have not resulted in significant weight loss. It is possible that lisdexamfetamine, through the modulation of prefrontal function, might lead to an additional improvement in inhibitory control and thus lead to weight loss. Prospective studies on weight changes with long-term treatment with active comparative treatments and evaluation of response inhibition function will be needed to clarify these mechanisms (McElroy et al., 2015).

Schag and colleague's review only considered behavioral tasks investigating food-related impulsivity (Schag et al., 2013), while we based our selection on standardized inhibitory control neurocognitive tasks. Our choice seems to be supported by the evidence for higher stop signal reaction time (SSRT) in obese participants without BED compared to controls, suggesting a general decrease in inhibitory function regardless of binge eating behavior. Another factor

could be related to the broader domain of "impulsivity" that Schag and colleagues investigated, in contrast to our more focused investigation on inhibitory control. Inhibitory control can be measured by specific neurocognitive tasks and depends on the activity of the PFC, and it seems particularly well suited to offer mechanistic insights into the regulation of eating behavior. As noted by Appelhans (Appelhans, 2009), a better understanding of inhibitory control can help us understand why some individuals, after starting a diet, manage to achieve successful dietary restraint while some do not. The reward value of food is unlikely to be diminished by the conscious decision to initiate dietary restriction, therefore the key element that leads to success in a diet is to exert sufficient inhibitory control (Appelhans, 2009). The ability to exert this control in everyday situations like buying food, preparing it or eating it during a meal are likely to be the concrete behaviors that mediate the effect of neurocognitive deficits in inhibitory control on BMI, in a similar manner to how self-control to substance-related cues in the environment affects the ability to abstain from substances in substance abusers (Blume and Marlatt, 2009).

4.2 Neuroimaging investigations

Studies comparing brain activation during inhibitory control tasks found reduced activation in the PFC (inferior frontal gyrus, ventromedial prefrontal cortex, dorsolateral prefrontal cortex) in obese participants with BED compared to obese participants without BED (Balodis et al., 2013; Hege et al., 2014). More prospective studies that compare obese participants with BED to

obese participants without BED are clearly needed to examine if abnormal prefrontal cortex activity is related to development of binge eating in obesity.

The studies investigating correlations between activity in inhibitory control-related brain function in areas, such as the PFC (superior and middle frontal gyrus, orbitofrontal cortex) and the inferior parietal cortex, and both current and future BMI found consistent negative correlations. Figure 4 summarizes the localization of these regions in the brain. The PFC is considered the key region involved in self-regulation. It represents goals and the means to achieve them, and it allows us to modulate our responses to environmental stimuli by exercising top-down inhibitory control (Miller and Cohen, 2001). Impairments of PFC function have been associated with eating dyscontrol and weight gain in many lesion studies (Freeman and Watts, 1950; Ikeda et al., 2002; Landtblom et al., 2002; Piguet, 2011; Regard and Landis, 1997; Whitwell et al., 2007), therefore the present results appear consistent with the well-known role of the PFC. The PFC showed low baseline metabolic activity in obese participants in studies with positron emission tomography (PET)(Volkow et al., 2009) and single-photon emission computed tomography (SPECT)(Willeumier et al., 2011). PFC hypofunctionality in obesity has also been suggested to be associated with lower gray matter volumes (Yokum et al., 2012). Other studies showed an increased PFC activity in successful dieters compared to controls in response to meal consumption (DelParigi et al., 2007). Also, less activation of the PFC in response to a meal in obese participants compared to controls (Le et al., 2007, 2006) suggest that reduced PFC function is responsible for a lack of inhibition of hedonic feeding in the obese participants (Appelhans, 2009). Our review indicates that standardized inhibitory control tasks index PFC activity and correlate with baseline BMI and future weight outcomes.

This framework could offer a mechanistic model for brain-based treatments for eating behavior in obesity. Inhibitory control could be a target for stimulation treatments that modulate PFC function in obese patients (Alonso-Alonso, 2013). Innovative and personalized treatment strategies can be developed by establishing the specific type of obese participants who can benefit from neuromodulation treatments.

4.3 Limitations

Due to slight variations in the specific names of the tasks (e.g. stop signal task, go-stop task, stop task; delayed discounting task, temporal discounting task), some studies might have been missed in our search. However, we believe that our thorough search procedure should have addressed this possibility. The level of heterogeneity detected in the meta-analysis in the comparison between obese participants without BED and controls could not be explained with the variables that we included in the meta-regression. This might be caused by partial reporting of these variables or by other variables that we could not identify. In this regard, it is important to note that obese participants compared to controls were not screened for binge eating in some studies included in the meta-analysis (Bongers et al., 2014; Hendrick et al., 2012; Nederkoorn et al., 2006), which could be a source of heterogeneity. However, the finding of inhibitory control deficits in obese participants without BED compared to controls seems unlikely to be driven by the presence of obese participants with BED in the sample, given that the direct comparison between obese participants with BED and obese participants without BED does not show worse inhibitory performance in obese participants with BED. There are few

studies that provide direct comparisons between obese participants with BED and obese participants without BED, therefore the results of this comparison have to be interpreted with caution. The reported studies used complex analytic approaches and were usually comprised of different procedures. For this reason, we were not able to describe in detail all the analyses and the results for each study, but we discussed those that were pertinent to the questions this review attempted to answer.

5.0 CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, we found sufficient evidence to support the presence of inhibitory control deficits in obese participants compared to controls. No significant differences in inhibitory control were found in obese participants with BED compared to obese participants without BED. Impairments in inhibitory control assessed with standardized neurocognitive tests appear thus to be associated with obesity independently from binge eating. Neuroimaging studies suggest that reduced function in an inhibitory network that has the PFC as the key region is related to current overweight and obesity and future weight gain.

Future behavioral and neuroimaging studies should include a group of obese participants without BED and a group of obese participants with BED in order to distinguish the neurocognitive features of obesity from those of binge eating. Future longitudinal studies should also test the relationship between inhibitory control and PFC activity in response to interventions, in order to define predictors of outcome and provide differential indications for treatment (i.e. individual indications for nutritional counselling, psychosocial interventions,

drug treatment, lifestyle change or combinations of these components). Knowing how inhibitory control affects response to treatment would allow to tailor the components of treatment interventions to the needs of the individual patient, as current emphasis on precision medicine mandates (Ashley, 2015). In light of the prominent role of PFC in inhibitory control and the alterations described, neuromodulation of the PFC holds promise as a targeted approach to improve inhibitory control as part of a comprehensive treatment strategy for the treatment of obesity (Alonso-Alonso, 2013; Cosmo et al., 2015).

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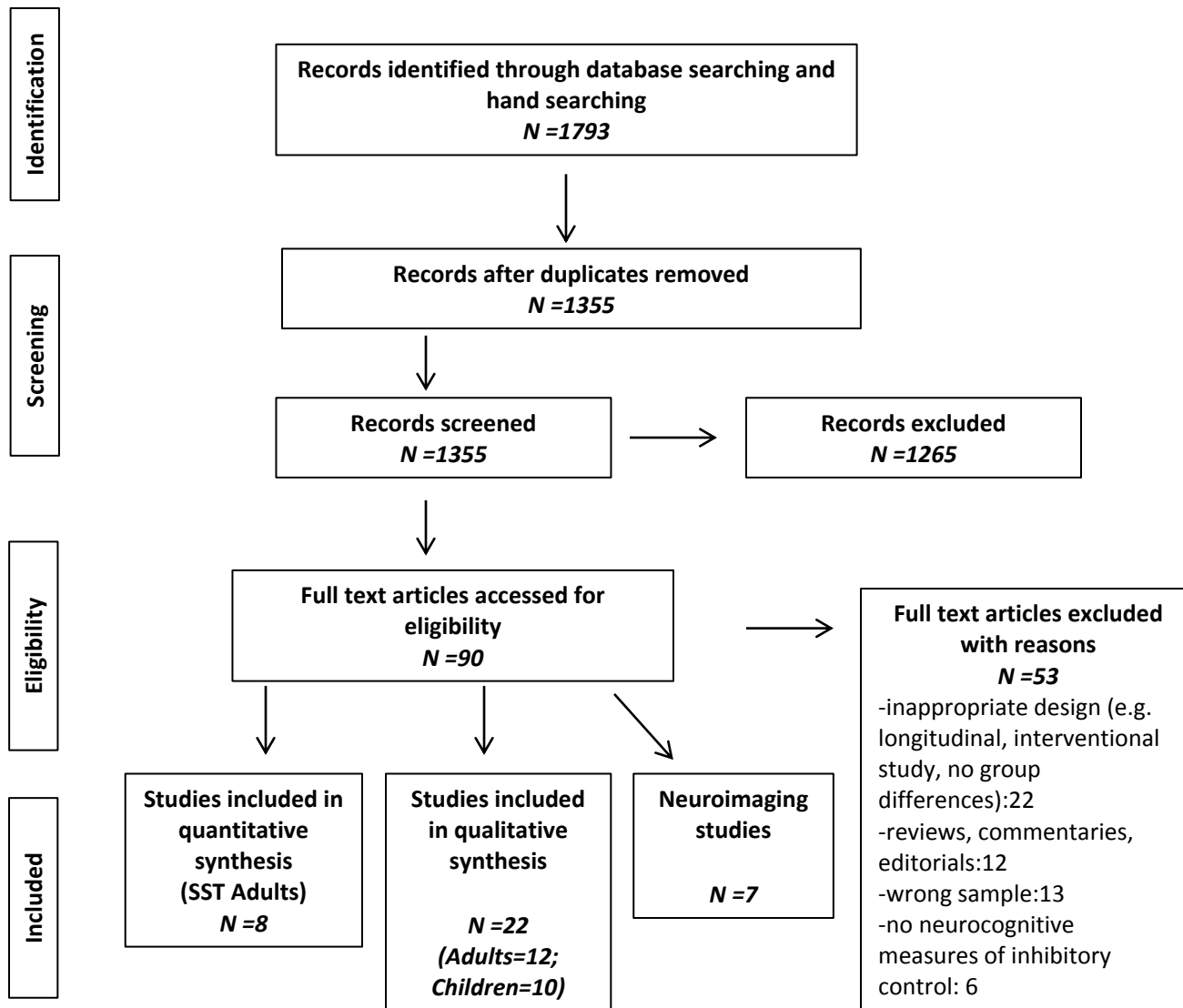
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"Figure 1. Flowchart illustrating the number of records identified and those included and excluded at each stage of the search."



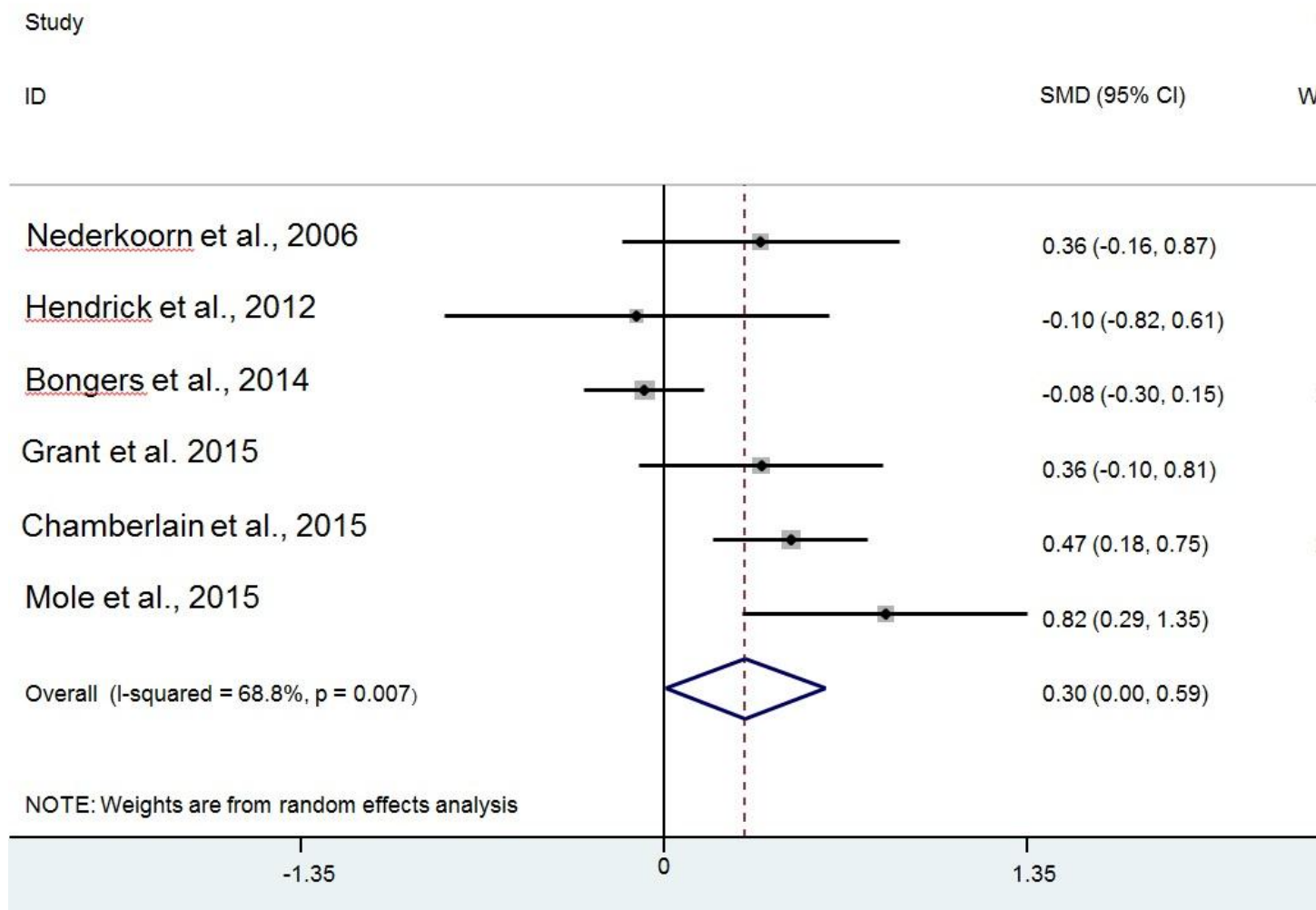


Figure 2 Forest plot for the summary effect size of the difference in the stop signal reaction time (SSRT) between obese subjects and controls

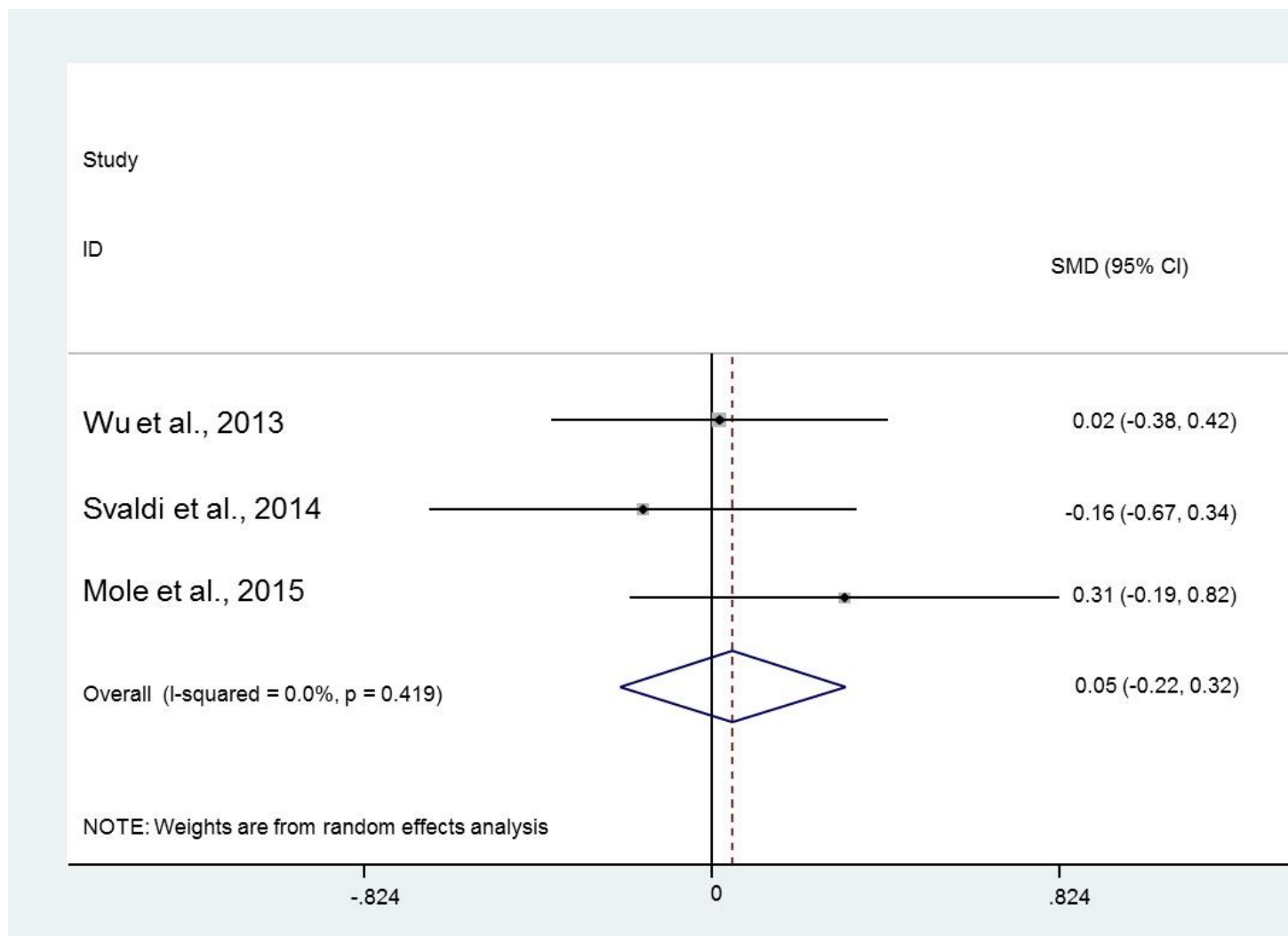


Figure 3 Forest plot for the summary effect size of the difference in the stop signal reaction time (SSRT) between obese subjects with BED and obese subjects without BED

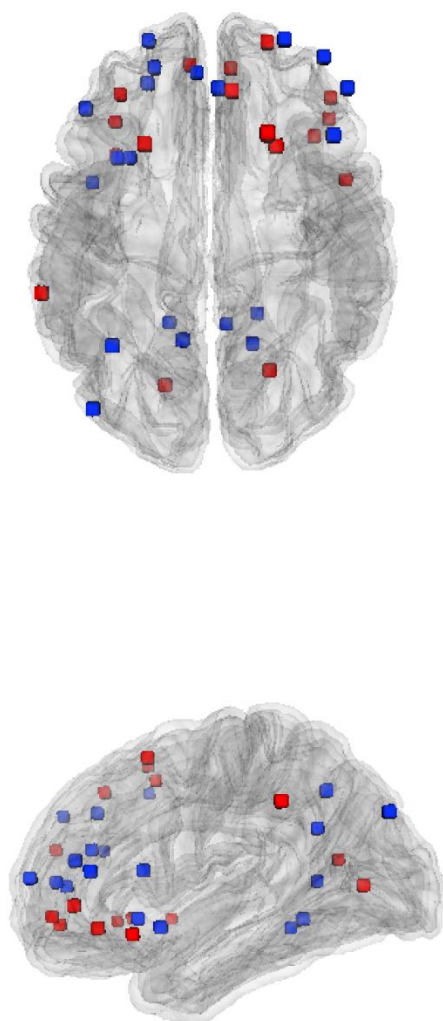


Figure 4 Schematic representation of brain areas where inhibitory control-related activity correlates with baseline (red squares) or future (blue squares) BMI (based on Batterink et al., 2010; Hendrick et al., 2012 and Batterink et al., 2010; Kishinevsky et al., 2012; Weygandt et al., 2015, 2013)

Table 1 Behavioral inhibition tasks in obese adults

Paper	Task	Subjects	OB/ NW	OB- BED/OB	Outcom e	Results	Quality score (x/8)
Nederkoorn et al. 2006 <i>m-a</i>	Standard SST, delay discounting	31 OB; 28 NW F	X		SSRT	OB>NW in the last blocks of the SST (no significance difference considering the task in its entirety). Delay discounting task: OB=NW	4
Weller et al. 2008	Delay discounting task	45 OB, 50 NW F	X		Delay discounti ng	Obese women showed greater delay discounting than control women. No difference was found in men	6
Duchesne et al. 2010	Stroop	OB-BED 38, OB 38 M<F		X	Errors, response times	OB-BED=OB	6
Davis et al. 2010	Delay discounting task	65 OB- BED; 73 OB; 71 NW F	X	X	Indiffere nce point	NW>OB-BED; NW>OB OB= OB-BED	5
Nijs et al. 2010	Food- related	20 OB, 20 NW	X		Reaction times	Reaction times for food stimuli	5

	Stroop, EEG	M<F				were longer than for non-food for all subjects; OB=NW	
Cohen et al. 2011	Stroop	42 OB, 107 NW M, F	X		Stroop color-word trial; Stroop interference score	The number of words completed in the color-word trial was lower in the obesity group; the Stroop interference was higher in the OB group	7
Mobbs et al. 2011	Food-body mental flexibility task (a food-specific go/no-go)	16 OB-BED, 16 OB, 16 NW M<F	X	X	N of errors	OB-BED>NW; OB>NW; OB-BED>OB	5
Galoto et al. 2012	Stroop	41 OB-BED, 90 OB M, F		X	Number of words correctly identified	OB-BED=OB	5
Loeber et al. 2012	Food-specific Go/no go task	20 OB, 20 NW M, F	X		Response times	All participants faster in responding to food compared to objects. No effects of category (food or object word), no effect of group, no categoryXgroup interaction	5
Hendrick et	Standard	18 NW,	X		SSRT	NW=OB	3

al. 2012 <i>m-a</i>	SST	13 OB F					
Fagundo et al. 2012	SCWT	52 OB, 137 NW F	X		Stroop interference score	OB<NW (OB have a worse performance)	8
Wu et al. 2013 <i>m-a</i>	Standard SST, GDT	19 BN, 54 OB- BED, 54 OB M<F		X	SSRT	OB-BED=OB	7
Svaldi et al. 2014 <i>m-a</i>	Food- specific SST	31 OB- BED, 29 OB F		X	SSRT, errors	OB-BED>OB in both SSRT and errors	7
Calvo et al. 2014	Go/no-go	32 NW, 30 OB M, F	X		Response time	OB>NW	4
Mole et al. 2014 <i>m-a</i>	Standard SST, delay discounting task	30 OB- BED; 30 OB, 30 NW M, F	X	X	SST: SSRT delay discounti ng task: slope of the discounti ng curve (k)	Delay discounting OB-BED>NW; OB>NW SSRT OB>NW; OB-BED<OB (=OB more	6

						impaired) OB-BED=NW	
Grant et al. 2015 <i>m-a</i>	Standard SST	NW 136; OW 49; OB 22 M, F	X		SSRT	OB>NW	7
Bongers et al. 2015 <i>m-a</i>	Standard SST, delay discounting task,	185 OB; 134 NW M<F	X		SSRT	Both in SST and in delay discounting: OB = NW	6
Manasse et al. 2015	SCWT (D-KEFS); Delay discounting task	31 OB-BED; 43 OB F		X	Inhibition time; level of discounting	Delay discounting: OB-BED<OB (steeper discounting in OB-BED)	5
						SCWT: OB-BED>OB	
Chamberlain et al. 2015 <i>m-a</i>	Standard SST	346 NW; 55 OB M, F	X		SSRT	OB>NW	6
Hume et al. 2015	Food-specific Stroop	41 NW, 19 OB F	X		Reaction times, errors	NW=OB	4

BN: bulimia nervosa; OB: Obese subjects; OB-BED: Obese subjects with Binge Eating Disorder; CN: Normal weight controls; SCWT: Stroop color-word test; D-KEFS: Delis-Kaplan Executive Functioning System; M=males, F=females; M<F=predominantly female sample; *m-a*: included in the meta-analysis.

Table 2 Behavioral inhibition tasks in obese children

Paper	Task	Subjects	Age (years)	Results	Quality score (x/8)
Nederkoorn et al. 2006	SST	15 OB-BED, 15 OB, 31 NW	12-15	SSRT: (OB-BED + OB)>NW	5
Verbecken et al. 2009	SST	41 OB, 40 NW	10-14	SSRT: OB >NW	7
Verdejo- Garcia et al. 2010	Stroop, delay discounting	27 OW; 34 NW	13-16	Stroop interference: OW>NW (P=0.07) Delay discounting: OW=NW	7
Maayan et al. 2011	SCWT	54 OB; 37 NW	16-19	Stroop interference score: OB<NW	5
Fields et al. 2011	Delay discounting task	16 OB, 20 NW (smokers)	13-19	Delay Discounting: OB>NW	4
Kamijo et al. 2012	Go/no go EEG	53 OB; 37 NW	7-9	No Go response accuracy: OB<NW	5
Nederkoorn et al. 2012	SST	14OW; 75NW	7-9	SSRT: OW>NW	6
Fields et al. 2013	Delay discounting task, go/stop task	21 OB; 20 OW; 20 NW	14-16	Delay discounting: OB>NW, OW>NW; SSRT: NW=OW=OB	7
Kulendran et al. 2014	SST	53 OB; 50 NW	10-17	SSRT: OB>NW	6

Reyes et al. 2015	Stroop, Go/no go	93 OB; 92 NW	10	Stroop test reaction time: OB>NW; Go/no go variability: OB>NW	6

OB: Obese subjects; OW: overweight subjects; NW: Normal weight subjects; SCWT: stroop color-word test; SST=stop signal task; SSRT=stop signal reaction time. All the samples were comprised by both males and females.

Table 3 Brain imaging (fMRI and MEG) Inhibition studies and BMI

Paper	Aim	Task	Subjects	Results
Batterink et al. 2010	correlations between inhibitory control-related brain activity and 1. Current BMI; 2. BMI Change in time	Food-specific go/no-go task	39 adolescent girls ranging from lean to obese.	Adolescents with higher BMI showed a higher rate of commission errors and reduced activation of frontal inhibitory regions (SFG, MFG, VLPFC, mPFC, OFC)
Kishinevski et al. 2012	correlations between inhibitory control-related brain activity and BMI change in time	General delay discounting	24 obese women	More difficult compared to easier DD trials activated frontal areas (MFG, IFG, mPFC); also, less activation in these areas in difficult VS easy DD trials predicted a greater rate of weight gain over the subsequent 1.3-2.9 years
Hendrick et al. 2012	group differences between OB and CN and between BED-OB and OB; Testing correlations between inhibitory control-related brain activity and	SST	18 lean women, 13 obese women	No statistical differences in performance measures. During the task lean women had greater activation in insula, inferior parietal cortex, cuneus, supplementary motor area in stop as compared to go trials. Brain activations in these regions inversely correlate with BMI

	BMI			across subjects
Balodis et al. 2013	group differences between OB and CN	SWCT	12 obese BED subjects; 13 non-BED obese; 11 CN	BED subjects showed diminished activity in VMPFC, IFG, insula. Dietary restraint correlates negatively with right IFG and VMPFC activation in BED subjects but not in obese or CN
Weygandt et al. 2013	Testing correlations between inhibitory control-related brain activity and BMI change in time	Food delay discounting	16 female subjects obese or overweight (BMI>27) and with overweight-related comorbidities	Higher behavioral impulse control was correlated with amount of weight loss after a 12 week diet. Brain activity before the diet in VMPFC and DLPFC correlated with subsequent weight loss. Stronger connectivity between these regions is associated to better dietary success and impulse control
Hege et al. 2015	group differences between BED-OB and OB	Food-specific go/no-go	18 BED obese women; 19 obese non-BED	Lower inhibition performance in BED; hypoactivity of the frontal control network during the inhibitory task
Weygandt et al. 2015	Testing correlations between inhibitory control-related brain activity and BMI change in time	Food delay discounting	23 obese females. <u>Method:</u> DDT at beginning of diet, end, and 1 year follow-up	Behavioral measures of control and DLPFC activity at T0 correlates with the degree of success in weight maintenance after 1 year. Neural signals correlate better with outcomes.

SCWT: Stroop color-word test; SST=stop signal task; DDT= delay discounting task; BMI=body mass index; SFG=superior frontal gyrus; MFG=middle frontal gyrus; VLPFC=ventro-lateral prefrontal cortex; mPFC=medial prefrontal cortex; OFC=orbitofrontal cortex; VMPFC=ventromedial prefrontal cortex; DLPFC=dorsolateral prefrontal cortex; DD=delay discounting. All the studies used fMRI except Hege et al. 2015 which used magnetoencephalography (MEG).